

Role of CEUS in the diagnosis of gallbladder disease

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Abstract

Conventional ultrasound (US) is the first imaging investigation recommended for diagnosis of gallbladder pathology. However, it has an important limit of ability to depict microcirculation of some biliary lesions which may lead to failure in diagnosis. The use of contrast-enhanced US (CEUS) seems to overcome these limits and allows a more confident diagnosis. In this review, the methodology, image interpretation, enhancement pattern, clinical usefulness, and indications for CEUS in gallbladder lesions are summarized. CEUS may be indicated under the following circumstances: 1) For differentiation diagnosis between a malign tumor or a benign tumor of the gallbladder; 2) to make a distinction between motionless sludge and gallbladder carcinoma; 3) to assess the extension of gallbladder carcinoma in adjacent hepatic parenchyma; 4) patients with impaired renal function.

Keywords: gallbladder tumors, ultrasound, contrast enhanced

Introduction

B mode ultrasound (US) is the first imaging investigation performed for the diagnosis of biliary pathology. It has a high sensitivity to detect gallbladder stones and intra-hepatic or extra-hepatic bile duct dilatation. The main limitation of ultrasound is a low ability to assess vascularity and therefore to establish the nature of gallbladder and biliary ducts tumors [1].

In generally gallbladder cancers present as either a solid mass that occupy the whole gallbladder or a focal polypoid lesion on conventional US. Also a motionless biliary sludge can generate similar US images with gallbladder cancer [2]. In these cases the presence of vessels can make the differential diagnosis between a benign le-

sion and gallbladder cancer. Color and power Doppler US have been developed to overcome these limitations but several limits still remained: a slow flow or deeply located blood vessels [1,2].

The introduction of micro-bubble contrast agents (UCA) and the development of contrast-specific imaging techniques have improved the performance of B mode US. Microbubble contrast agents have diameters in the range of 1–10 μ m (median 2 μ m) that do not allow filtering by the lungs or the entering into the interstitial fluid. Therefore, they are completely intravascular contrast agents. Having this feature they give an accurate assessment of the blood flow within a lesion and permit the diagnosis of the nature of that lesion. Another important feature is that micro-bubbles agents are not radioactive. SonoVueTM micro-bubbles are composed of a sulphur hexafluoride gas with a phospholipids shell. The contrast agents are metabolized by the liver and the sulphur hexafluoride gas is exhaled via the lungs.

After several studies showed that the utilization of contrast-enhanced ultrasound (CEUS) substantially improves the detection and the characterization of gallblad-

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der lesions [2-5], in 2011 CEUS was accepted in the *Guidelines and good clinical practice recommendations for CEUS* - update 2011, for clinical practice [6].

Scanning method

Each patient has to be fasted for least 8 hours before examination. Before performing a CEUS examination, the gallbladder and adjacent liver parenchyma should be examined using conventional gray-scale US and the target lesion identified. After identification of the target lesion, the transducer is kept in a stable position and the imaging mode is changed to low mechanical index ($MI < 0.2$). The tissue signals are eliminated and the depth, gain and focus are carefully adjusted. UCA is administered intravenously through the antecubital vein as a bolus (within 1-2 s), followed by a flush of 10 ml 0.9% sodium chloride solution. The timer should be activated from the beginning of contrast agent administration and the lesion is observed intermittently for at least 3 min. It is important that the entire CEUS process for the intrahepatic biliary system should be performed with reference to the adjacent liver parenchyma [2].

CEUS – enhancement pattern of gallbladder

The vascular phases of the gallbladder are different from those of the liver because the blood supply is provided entirely by the cystic artery and not by portal vein branches. Therefore only 2 phases can be followed: arterial phase (10–20 s after bolus injection) and late phase (31–180 s after contrast injection). The late phase persists for a short time in comparison with that for the liver [7,8]. Enhancement is assessed by comparing the echogenicity of a lesion with the echogenicity of the liver parenchyma.

Pathology

1. Polypoid lesions of the gallbladder

The majority of polypoid lesions of the gallbladder are cholesterol polyps. US has 90% sensitivity for the detection of polypoid lesions. Distinguishing a potentially pre-malignant adenoma from a benign cholesterol polyp is not possible always only on the basis of US. There are several features that can suggest the benign nature of polypoid lesions: size less than 10 mm, multiplicity and an increased echogenicity. By contrast, increasing size on sequential US examinations, focal thickening of the gallbladder wall or nodularity adjacent to a polypoid mass can suggest malignancy.

The US appearance of cholesterol polyps is that of multiple, non-shadowing, oval lesions attached to the gallbladder wall. The size is usually 2-5 mm and the diagnosis is made easily with US. Larger lesions (up to 20

mm) should be differentiated from adenomas or gallbladder carcinomas [9].

On CEUS, hyper-enhancement is found in the majority (93%) of the lesions and the remaining 7% show iso-enhancement during the early phase. In cholesterol polyps, normal-caliber arteries taper normally and subdivide normally into small vessels, thereby the lesion shows dotted- or branched-type tumor vessels on CEUS. In the late phase, hypo-enhancement is found in 64% and iso-enhancement in 36% of the lesions [2,7] (fig 1).

2. Gallbladder adenomas

Gallbladder adenomas are relatively uncommon, with an incidence ranging between 0.3% and 0.5% in gallbladders removed [7]. Gallbladder adenoma appears on US as a sessile polypoid mass, with an echogenicity slightly greater or similar to the liver, with a smooth or lobulated surface and a relatively homogeneous internal texture, without infiltration to the adjacent tissue. On CEUS examination adenomas can appear during the early phase homogeneous hyper-enhanced (78%) and iso-enhanced (22%). In the late phase they appear iso- (56%) and hypo-enhanced (44%) [2] (fig 2).

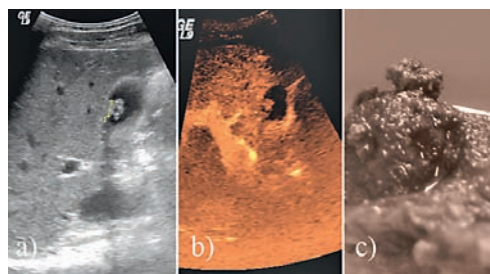


Fig 1. Cholesterol polyps. a) Conventional US depicts one echogenic lesion arising from the gallbladder wall (<). b) CEUS image at 15 s after CA administration demonstrates vascularity of the lesion; c) macroscopic specimen.

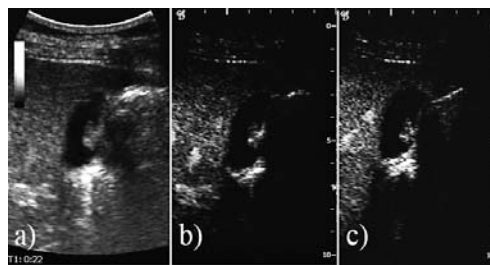


Fig 2. Gallbladder adenoma. a) B mode US shows an echogenic mass arising from the wall; b) in arterial phase the lesion is iso-enhanced in respect with the liver; c) in venous phase the lesion is slightly hypo-enhanced.

3. Gallbladder sludge

Gallbladder sludge is a mixture of particulate matter and bile that occurs when the solutes in bile precipitate. In the differentiation between gallbladder cancer and motionless biliary sludge CEUS has a sensitivity of 100% [2,4]. Because of the lack of vessels in the arterial phase the mass will appear non-enhanced. In the late phase it will remain non-enhanced (fig 3).

4. Adenomyomatosis

Adenomyomatosis is a hyperplastic cholecystoses, has no malignant potential and may involve the gallbladder in a focal, segmental or diffuse form.

It is relatively commonly found in 1-9% of all cholecystectomy specimens and is characterized pathologically by hyperplasia of the wall with formation of intramural mucosal diverticula (Rokitansky-Aschoff sinuses) penetrating into the muscular wall of the gallbladder, with or without gallbladder wall thickening.

On US examination the characteristic feature is the comet tail artifact echogenic intramural foci from which emanate *V-shaped "comet tail" reverberation artifacts*. Those artifacts represent the unique acoustic signature of cholesterol crystals within the lumina of Rokitansky-Aschoff sinuses [1,7,8,10]. At CEUS examination in the arterial phase the gallbladder wall has a characteristic "moth-eaten" enhancement: the non affected gallbladder wall is normally enhanced and the diverticulum zone will not depict contrast enhancement [8,10].

5. Acute cholecystitis

Acute cholecystitis is an inflammation of the gallbladder wall typically caused by a calculus obstructing the cystic duct. On CEUS examination during the arterial phase, enhancement of the gallbladder wall will be seen earlier than the enhancement of the adjacent liver parenchyma. In the late phase the thickened gallbladder wall will have an obvious "wash-out" comparative with the liver parenchyma (Figure 4). CEUS examination has an important role in detecting abscess formation in the surrounding liver parenchyma. Interruption of the gallbladder wall suggests perforation, which can be confirmed by the absence of enhancement of the perforated wall [2,3,8,6] (fig 5).

6. Gallbladder malignant tumors.

Gallbladder carcinoma is the fifth most common malignancy of the gastrointestinal tract and has an association with gall stones [8]. On US examination it can appear like a polypoid intraluminal lesion, a tissue mass infiltrating the gallbladder wall and the surrounding hepatic parenchyma or a diffuse mural thickening [1,9].

On CEUS examination, the arterial branches that supply the gallbladder carcinoma tend to show irregularly tortuous extension. The late phase washout of the con-

trast agent within 35-60 seconds after administration may be a key for differential diagnosis [2] (fig 6). Improved gallbladder wall visualization following contrast administration and the malignant feature of late-phase hypovascularity relative to the hepatic parenchyma may provide sharp demarcation of tumor outline.

Another appearance that can be seen in gallbladder carcinoma is a disruption of the gallbladder wall integ-

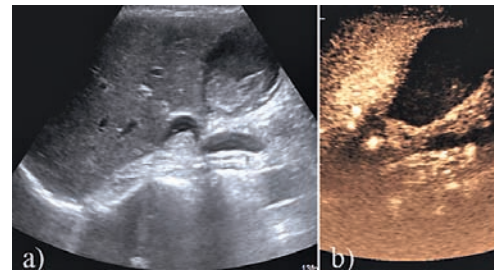


Fig 3. Gallbladder sludge. a) B mode US shows a gallbladder with an echogenic mass inside; b) CEUS in arterial phase depicts no enhancement within the mass.

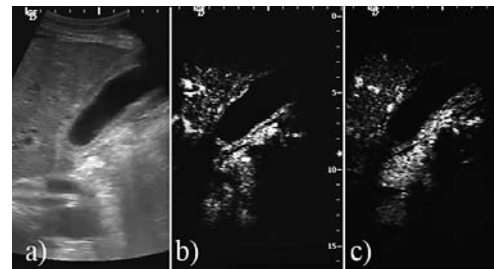


Fig 4. Acute cholecystitis a) B mode US in a patient after endoscopic stent placement shows a thickened, double layer gallbladder wall; b) in arterial phase the wall is hyperenhanced; c) in venous phase the wall becomes slightly hypoenhanced.

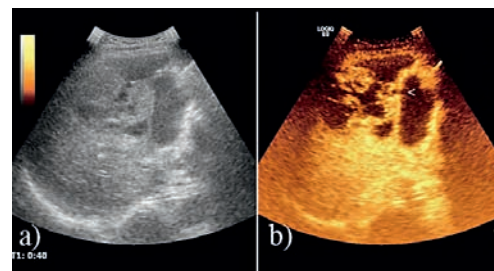


Fig 5. Acute cholecystitis with perforation and abscess formation. a) US shows a gallbladder with thickened wall and an irregular anechoic structure in the adjacent liver; b) CEUS in arterial phase depicts the hyperenhanced wall and a small disruption of the wall (<).

rity. On CEUS examination, in the arterial phase the wall disruption is better visualized [8] (fig 7).

Metastases to the gallbladder are very rare, the most common tumor leading to a metastatic tumor of the gallbladder being malignant melanoma. The lesions are usually multiple, hyperechoic broad base polypoid lesions larger than 10 mm [9]. The lesions are hyperenhancing in arterial phase with a rapid wash out (fig 8).

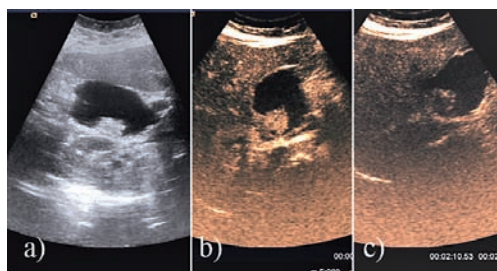


Fig 6. Small gallbladder carcinoma. a) conventional US shows a 2 cm polypoid mass in the gallbladder; b) in arterial phase CEUS depicts hypervascularity of the mass; c) in venous phase the mass becomes slightly hypo-enhanced.

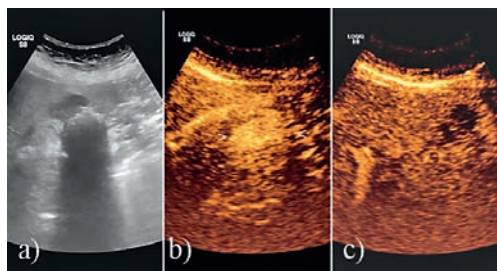


Fig 7. Gallbladder carcinoma with disruption of the wall integrity and invasion in liver parenchyma. a) US depicts a gallbladder full with stones, the walls could not be identified. In the adjacent liver a hypoechoic mass is well seen; b) CEUS shows a hyperenhanced lesion in arterial phase with c) wash out in venous phase.

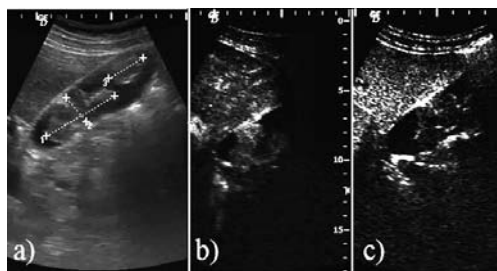


Fig 8. Gallbladder metastasis from melanoma. a) US shows a multiple, irregular masses in the gallbladder lumen; b) CEUS arterial phase, one lesion is hyperenhanced; c) in venous phase there is a clear wash-out.

7. Difference between benign and malignant lesions.

All gallbladder tumors, benign or malign, are supplied by arterial vessels from branches of the cystic artery. Therefore in the arterial phase most of the lesions are hyper-enhanced in the early phase of CEUS and no difference between them is detected [2,5]. Hyper-enhancement in the arterial phase was present in 84.8% of carcinomas and in 70.2% of benign lesions (92.2% cholesterol polyps, 77.8% adenomas and 85.5 % chronic cholecystitis) [7].

The distribution of the vessels inside the lesion may add some diagnostic features. Thus, the benign lesions show dotted vessel enhancement whereas malignant lesions tortuous vessel enhancement [7].

Although the late phase is important in establishing the nature of the hepatic lesion, for gallbladder this algorithm is not always applicable. Nevertheless wash-out phenomenon of the contrast agent within 35-60 s after UCA administration was present mostly in malignant tumors [5].

Disruption of the gallbladder wall integrity appears in 85% of gallbladder carcinomas and in none of the benign lesions (specificity 100%).

The combination of enhancement pattern (hyper-enhancement or iso-enhancement in the early phase with hypo-enhancement within 35 s after contrast agent administration) and lesion's size yield a sensitivity of 90.9%, specificity of 87.2% and an accuracy of 88.8 % in diagnosing malignancy [2].

8. Conclusions

In the diagnosis of gallbladder lesions CEUS overcomes the limitations of conventional US and allows an improved ability in the assessment of intralesional vascularity. CEUS is a safe method that has proved to have a high accuracy in the diagnosis of gallbladder lesions. Also it has proved to be a trusted tool in differentiating malignant and benign tumors.

In clinical practice CEUS may be used in the following settings: 1) For patients with renal impairment for whom the use of contrast agents in CT imaging is not allowed; 2) To make a differential diagnostic between a malign and a benign tumor of gallbladder; 3) To make a differential diagnostic between motionless sludge and gallbladder carcinoma; 4) To assess the extension of gallbladder carcinoma in adjacent hepatic parenchyma.

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